Grantsmanship Recommendations

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Before you write a grant....

... understand the system
(R01 & R21)

NIH Exploratory/Developmental Research Grant Award (R21)

Encourages new, exploratory and developmental research projects by providing support for the early stages of project development. Sometimes used for pilot and feasibility studies.

Limited to up to two years of funding.

Combined budget for direct costs for the two year project period usually may not exceed $275,000.

No preliminary data generally required.

Research Project Grant Program (R01)

NIH's most commonly used grant program.

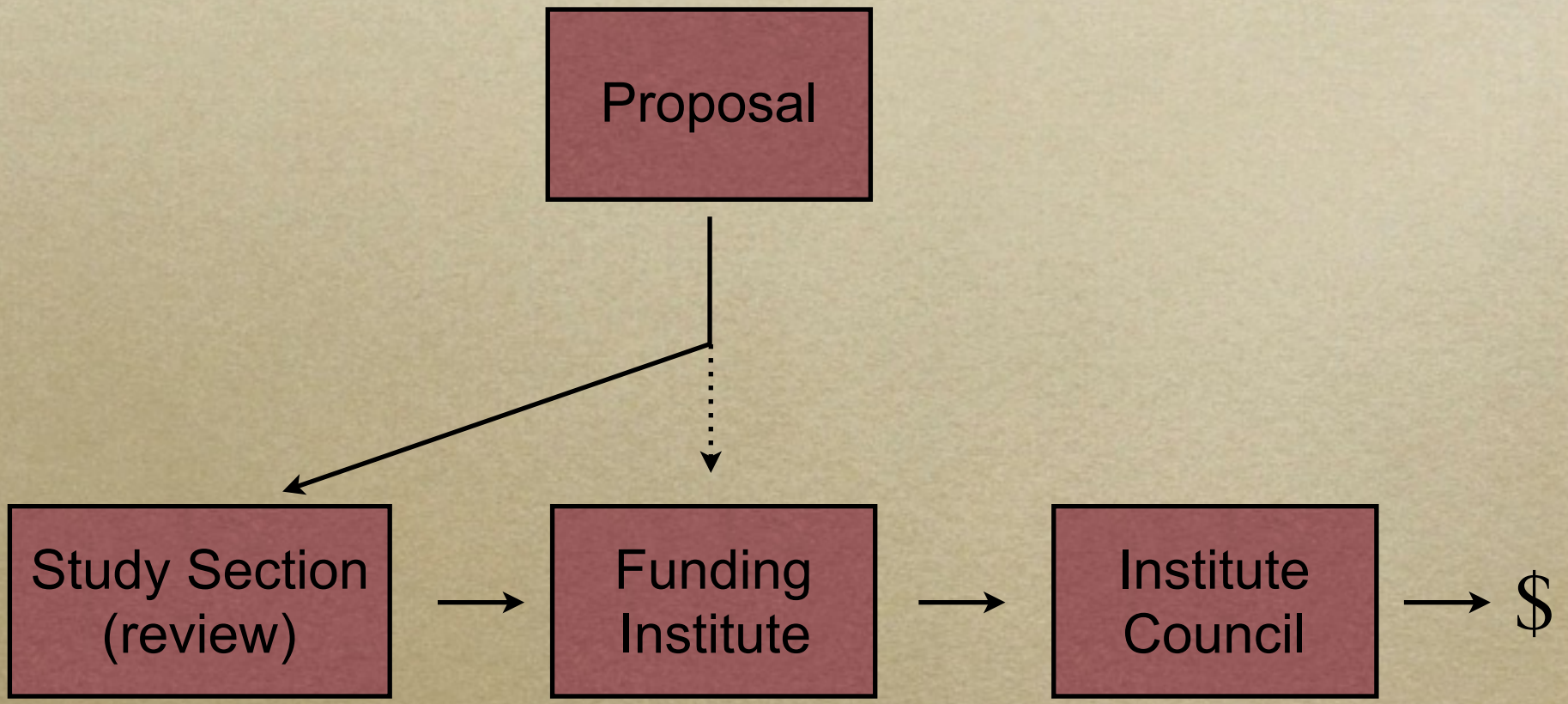
Used to support a discrete, specified, circumscribed research project.

No specific dollar limit unless specified in announcement.

Advance permission required for $500K or more (direct costs) in any year.

Generally awarded for 3 - 5 years.

NIH Review Process



CONSIDER THESE CRITERIA WHEN FORMULATING YOUR RESEARCH IDEAS

SCORED REVIEW CRITERIA

- Significance
- Investigator(s)
- Innovation
- Approach
- Environment

- OVERALL IMPACT
  - **NOT** average of individual core criteria

SIGNIFICANCE

- Does the project address an important problem or a critical barrier to progress in the field?
- If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
- How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

INNOVATION

- Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?
- Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?
- Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?
- Note: Not all applications have to be innovative.

APPROACH

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Are potential problems, alternative strategies, and benchmarks for success presented?
- If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

ENVIRONMENT

- Will the scientific environment in which the work will be done contribute to the probability of success?
- Are the institutional support, equipment, and other physical resources available to the investigators adequate for the project proposed?
- Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

INVESTIGATOR(S)

- New Investigator (NI)
  - PI who has not yet competed successfully for a substantial NIH research grant
  - If multiple PD/PIs - all PD/PIs must meet requirements for NI status.
- Early Stage Investigator (ESI)
  - PI who qualifies as a New Investigator AND is within 10 years of completing the terminal research degree or is within 10 years of completing medical residency (or equivalent)

OVERALL IMPACT

"Assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved"

"An application does not need to be strong in all categories to be judged likely to have major scientific impact."

Before you write a grant...

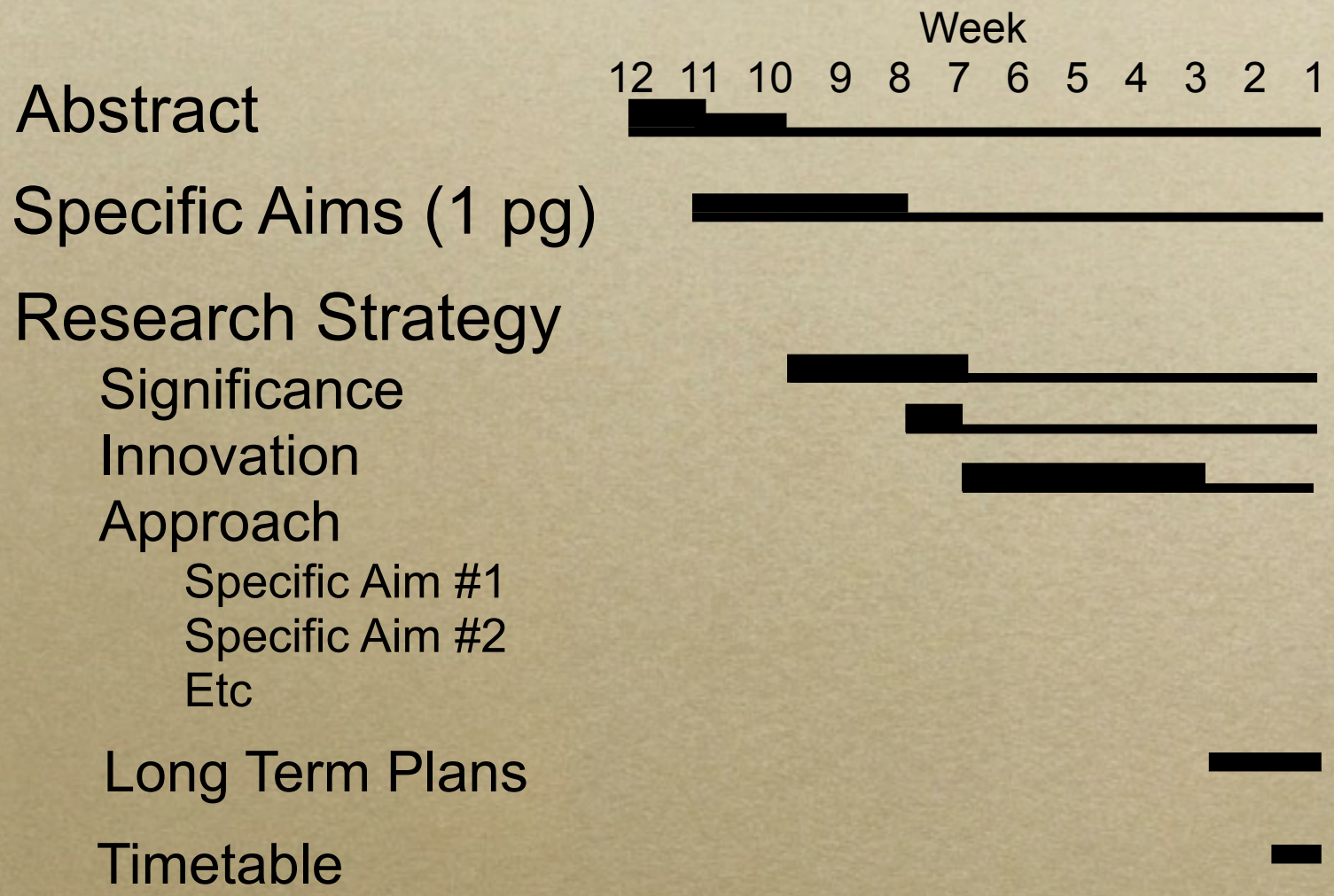
- **Identify a *significant* problem/area** -- Will successful studies lead to a paradigm shift?
- **Get preliminary data** -- Use your start-up; know when you have enough preliminary data (but not too much!)
- **Plan ahead** -- Start writing 6 months ahead of deadline. *Dedicate 20 hrs/week for last 3 months*.

Before you write a grant...

- **Study successful proposals** -- *Get grantsmanship ideas from advisors, etc.*

- **Write for the reviewers** -- *Each of the five criteria must be explicitly addressed in a format that makes it EASY for the reviewers to locate that information!*

NIH Proposal Layout and Effort



Writing Recommendations

1. ***Assume the reviewers don't know anything***
   - *Detailed background*
   - *Limit and explain jargon*
   - *Easy to read, especially the abstract and introductory material. Why is the work important?*

Writing Recommendations

2. ***Assume the Reviewers are Smart***

   - *Reasonable objectives*
   - *Reasonable budget*
   - *Do preliminary data adequately address feasibility?*

Abstract

The goal of the proposed studies is to determine how retroviruses select and package their diploid RNA genomes.

Sample NIH-funded Abstract (3.5 percentile)

First sentence:
describe the overall goal

Abstract

During the current funding period, we obtained strong *in vivo* and *in vitro* evidence that the Moloney Murine Leukemia Virus (MLV) uses an RNA structural switch mechanism, in which high affinity nucleocapsid (NC – the protein domain responsible for genome selection) binding sites are sequestered by base pairing in the monomeric RNA and become exposed to allow NC binding upon dimerization.

Second sentence:
Current State of the Field

Abstract

Having nearly completed studies of this model retrovirus, we now intend to focus almost exclusively on the Human Immunodeficiency Virus (HIV-1).

Third sentence:
How the current state of the field relates to your proposal

Next sentences: Exciting unpublished preliminary findings and how they relate to the proposed studies

Methods developed over the past 3 ½ years now enabled us to obtain NMR spectra of outstanding quality for the intact HIV-1 5'-UTR in its monomeric (356 nucleotides) and dimeric (712 nt) states. Based on these and other unpublished findings, we now believe that genome dimerization and packaging are mediated by a novel allosteric “nucleotide displacement” RNA switch mechanism, in which residues near the *gag* start codon induce a global rearrangement that simultaneously exposes a dimer-promoting stem loop (DIS) and high affinity NC binding sites that were sequestered in the momomeric conformer. Preliminary *in vivo* packaging experiments support this mechanism. 5'-UTR mutants that exclusively adopt either the monomer or dimer conformation have been prepared, and NMR spectra of outstanding quality have been collected for these constructs.

Concluding sentence:
Exciting unpublished preliminary findings and how they relate to the proposed studies

We are thus poised to determine the high-resolution 3D structure of the HIV-1 5'-UTR in conformations relevant to the mechanism of diploid genome selection.

Finish with a strong impact statement

NMR studies of such large RNAs are technically challenging – the average size of all NMR-derived RNA structures in RNA Structure Database is only 25 nucleotides – but the potential payoff is substantial, and could ultimately lead not only to a more detailed understanding of how HIV replicates, but also to the development of new approaches for the treatment of AIDS, cancers, and other virally-induced human diseases.

A weaker abstract

Abstract

Two, three and four-dimensional NMR methods, including sophisticated 13C-,15N-heteronuclear correlated multiple quantum coherence methods, will be used to study the structure and dynamics of large portions of the HIV-1 5'-UTR. We will use a specific labeling strategy that involves ligation of natural abundance and 13C-isotopically labeled RNA fragments using T4 RNA ligase, which will allow us to specifically examine residues that overlap with the 5'-UTR-Gag junction. NMR data will be analyzed with NMRView, and structures will be determined using AMBER with force fields that either explicitly or implicitly account for water molecules and cations.....

Lacks an overall goal statement

Too many specific details for an abstract

Too much jargon

No motivating background/rational

No exciting preliminary work or justification

2. Specific Aims

Nuclear magnetic resonance (NMR) and other biophysical methods will be used to determine the three dimensional structure of the HIV-1 5'-untranslated region (5'-UTR) in its monomeric and dimeric states. Interactions that regulate the monomer-dimer equilibrium will be determined, residues that bind to the cognate nucleocapsid protein (NC) identified, and mechanistic hypotheses based on the structural findings will be tested *in vivo* using virus replication and genome packaging experiments. Studies of viruses with smaller encapsidation signals (Moloney Murine Leukemia (MLV) and Bovine Leukemia (BLV) viruses), which helped pave the way for the proposed HIV project, will be completed.

(1) HIV-1

(i) The structure of the dimeric HIV-1 5'-UTR will be determined. Preliminary studies indicate that the native RNA exists as a mixture of monomeric and dimeric species, and that dimerization exposes high-affinity NC binding sites. NMR spectra of high quality have been obtained for ^{13}C- and ^{2}H-labeled RNA constructs, including the 712 nucleotide dimeric 5'-UTR, demonstrating that high-resolution structural studies are feasible. Major goals are to identify interactions that stabilize the dimer conformation and expose the NC binding sites.

(ii) NC binding sites in the dimeric HIV-1 5'-UTR will be identified. Preliminary isothermal titration calorimetry (ITC) experiments indicate that the monomeric HIV-1 5'-UTR binds 7 ± 1 NC molecules with high affinity, whereas the dimer contains 32 ± 2 high affinity NC binding sites. Major goals will be to identify the high affinity NC binding sites, determine if NC molecules bind different sites in a preferred order, and establish structural features at the NC:RNA interfaces.

(iii) The structure of the monomeric HIV-1 5'-UTR will be determined. Preliminary studies indicate that the GC-rich loop of the dimer-promoting DIS hairpin base pairs with an upstream element (U5) in the monomeric 5'-UTR. NMR studies of constructs that contain strategic G-C to A-U substitutions will be conducted, which should allow rapid probing for these interactions in the intact 5'-UTR. 3D structural studies will be conducted to identify interactions that sequester a large number of NC binding sites.

(iv) The effects of NC on the monomeric HIV-1 5'-UTR will be studied. Our preliminary studies suggest that NC does not promote dimerization of the 5'-UTR exclusively *via* its inherent chaperone activity, as is commonly believed, but instead, shifts the equilibrium position by binding to specific high-affinity sites on the monomer. Thus, we believe there are two general groups of NC binding sites: a small number of sites that are exposed in the monomer that function by promoting NC-dependent dimerization, and those that only become exposed upon dimerization, possibly to bind a critical number of Gag molecules that are required to initiate virus assembly. NMR-detected NC titration experiments will be performed using 5'-UTR mutants that are trapped in either the monomeric or dimeric conformation.

(v) The packaging mechanism will be tested *in vivo* by site directed mutagenesis/genome packaging and viral replication experiments. We will study packaging efficiencies under single-copy transfection and infection conditions with vectors that contain the native 5'-UTR and mutants that form stable monomers or dimers *in vitro*. Experiments will also be designed and performed to test the hypothesis that, in addition to regulating diploid genome packaging, the conformational equilibrium may serve as a regulator of splicing and/or translation.

(2) Model Retroviruses

The 3D structure of the dimeric MLV Core Encapsidation signal ([?]^{CES}) will be determined using a combined NMR/cryo-electron tomography (cryo-ET) approach that we are helping develop (see below). The major goal is to establish the structure and function of essential "kissing" hairpins in the conserved core encapsidation signal ([?]^{CES}) of the viral 5'-UTR. NC binding and structural studies of an unusual packaging element from the Bovine Leukemia Virus (BLV) 5'-UTR will be completed. The primary goal of this work is to identify commonalities and differences among packaging mechanisms that are utilized by evolutionarily distinct retroviruses.

(3) Methodologies for Structural Studies of Larger RNAs

Efforts will be continued (with Wah Chiu at Baylor) to develop a combined NMR/cryo-electron tomography (cryo-ET) approach for determining structures of large retroviral 5'-UTRs and their complexes with NC and Gag proteins. Good preliminary fits of 3D tomographic reconstructions with NMR-derived coordinates have recently been obtained for the MLV core encapsidation signal (200 nucleotides). Upon completion of these studies, the approach will be extended to the intact HIV-1 5'-UTR. Continued efforts will also be made to develop improved NMR methods for structural studies of relatively large retroviral RNA packaging signals.

2. Specific Aims

Nuclear magnetic resonance (NMR) and other biophysical methods will be used to determine the three dimensional structure of the HIV-1 5'-untranslated region (5'-UTR) in its monomeric and dimeric states. Interactions that regulate the monomer-dimer equilibrium will be determined, residues that bind to the cognate nucleocapsid protein (NC) identified, and mechanistic hypotheses based on the structural findings will be tested *in vivo* using virus replication and genome packaging experiments. Studies of viruses with smaller encapsidation signals (Moloney Murine Leukemia (MLV) and Bovine Leukemia (BLV) viruses), which helped pave the way for the proposed HIV project, will be completed.

Opening paragraph:
Overview of what you plan to do

Next: List each aim and what the specific studies are proposed to accomplish

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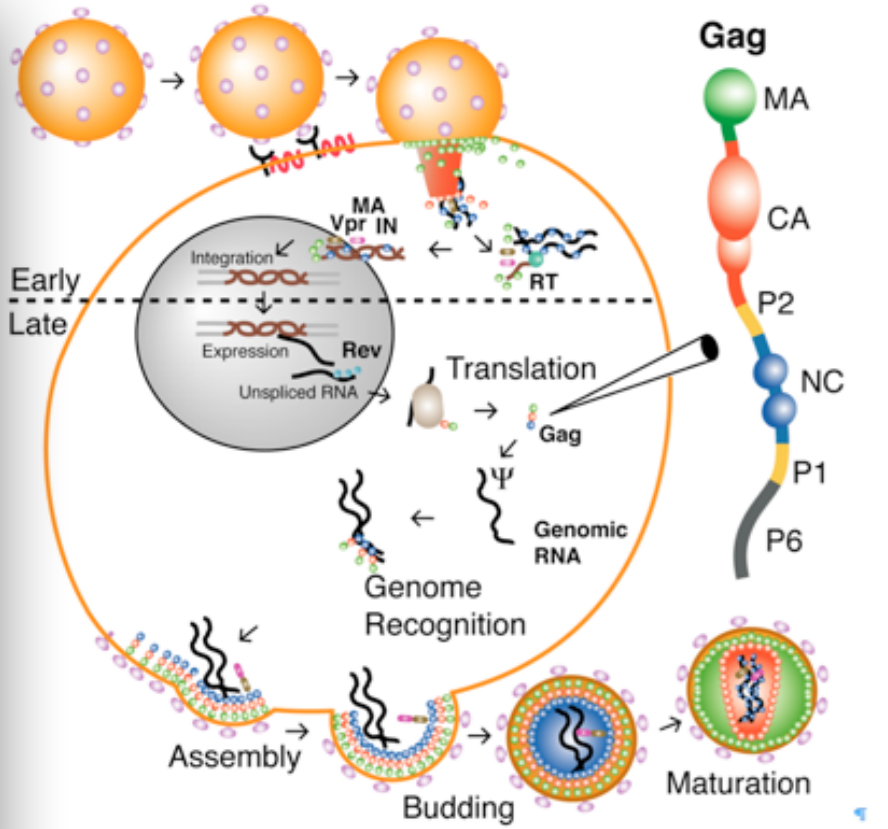
Background and Significance

Up-front overview:

cartoon, jargon, definitions.



one out of twenty adults are HIV positive (UNAIDS, 2007). According to the U.S. Centers for Disease Control, HIV infection rates in several major cities in the U.S., including Washington D.C., are equal to those in some sub-Saharan African countries. African Americans are disproportionately affected in the U.S., comprising 50% of the HIV-infected population. Drugs that target the HIV protease, reverse transcriptase, integrase, and

Figure 1. General features of the retroviral replication cycle. Two copies of the full-length RNA genome are specifically packaged (see definitions below):

Gag: Structural protein, ~2,000 copies assemble to form a virus particle.

NC: Domain of Gag that recognizes the genome.

Ψ-site: RNA element(s) generally located in the **5'-Untranslated Region (5'-UTR)** that are responsible for genome selection and packaging.

3. Background and Significance

Retroviruses are responsible for a variety of animal diseases, including leukemia, cancer, and Acquired Immunodeficiency Syndrome (AIDS). They can incorporate modified cellular genes during replication that confer tumorogenicity, induce neoplastic transformations upon integration of the proviral DNA into or near important cellular genes, interfere with normal cellular functions, or induce premature cell death[2]. Approximately 7-8% of the human genome consists of human endogenous retrovirus sequences (HERVs) that appear to have resulted from early infections and incorporation into the germ line[3], some of which have evolved important human functions[4]. The human immunodeficiency virus (HIV, the causative agent for AIDS[5-7]) is a particularly lethal retrovirus that has caused nearly 25 million deaths over the past 20 years. Approximately 33 million additional individuals are currently living with HIV, and in sub-Saharan Africa, one out of twenty adults are HIV positive (UNAIDS, 2007). According to the U.S. Centers for Disease Control, HIV infection rates in several major cities in the U.S., including Washington D.C., are equal to those in some sub-Saharan African countries. African Americans are disproportionately affected in

HIV, and in sub-Saharan Africa, one out of twenty adults are HIV positive (UNAIDS, 2007). According to the U.S. Centers for Disease Control, HIV infection rates in several major cities in the U.S., including Washington D.C., are equal to those in some sub-Saharan African countries. African Americans are disproportionately affected in the U.S., comprising 50% of the HIV-infected population. Drugs that target the HIV protease, reverse transcriptase, integrase, and envelope protein are currently available, and combination therapies can keep the virus at bay for extended periods. However, it appears unlikely that the current repertoires will lead to a cure, as the virus can be maintained in reservoirs that are not susceptible to the current drugs[8-15]. Current therapeutic regimes are expensive and compliance is difficult, and a number of strains that are resistant to combination drug therapies have emerged[16-19]. Thus, there is a need for new antiviral agents that target different viral components.

One potential target that has not been fully exploited is machinery involved in genome recognition and packaging. Genomes are selected for packaging during the Late phase of the viral replication cycle by the nucleocapsid (NC) domains of the retroviral Gag polyproteins (Fig. 1)[20-23]. NC domains contain “zinc knuckles”

Other Recommendations

Get Exposure Before Review

- *Contact meeting organizers once you have exciting preliminary data…try to get into an oral session*

- *Poster Abstracts at Major Conferences*

Get Experience: EARLY CAREER REVIEWER (ECR) PROGRAM

ECRs will participate in a CSR study section meeting once a year for up to two years.

ECRs will have a limited role, serving as the third reviewer on two NIH grant applications each time.

An ECR does not necessarily need to have NIH or equivalent funding.

Not just a training program. NIH wants ECRs to complement reviews.

CSREarlyCareerReviewer@mail.nih.gov

Final comments when starting a lab....

Focus on something new

- avoid competing with past advisers.

Don't focus initially on writing lots of grants

- use start-up to get exciting preliminary data.

Use New Investigator status wisely (R01 versus R21).

Rely on **yourself** for results, not your new students.

Don't try to build a large lab

- be a good mentor to **a few** promising students.

Final comments
When starting a lab....

Don’t teach lots of new courses.

When teaching, **multitasking** is critical

- develop and stick to a teaching/research schedule.

Don’t doubt your abilities

- **you made it this far because you are really good!**

The Awesomest 7-Year Postdoc or: How I Learned to Stop Worrying and Love the Tenure-Track Faculty Life

Scientific American, July 21, 2013

Radhika Nagpal,
now tenured at
Harvard

I stopped taking advice.

I hate to say this, but people lie. Even with the best intentions. If you ask them what is important to succeed as a junior faculty member, people will tell you everything they did that they think helped them succeed. Plus everything they wish they had done. And all the things their friend did too. They deliver you this list without annotation, a list which no single person could ever accomplish. And while this list sends you into shock, followed by depression, followed by a strong desire to quit (because heck I'm never gonna be able to do all that) -- the truth is that that is the last thing this person wants. They want you to succeed! **And so with the best of intentions, they advise you on how to fail.**

An extreme case… To make a long story short, several senior women got up and explained how we needed to do all the things the male junior faculty were doing, but then also do a whole second list of extra things to compensate for the fact that there is huge implicit bias against women in letters and assessments. And there I was, with two young kids, already worried how I was going to have to be twice as productive as the men in order to compete with half as many working hours. **And these women were telling me I'd have to be four times as good as the men per hour to survive! These women had the best of intentions. But I came back to my office, lay on the couch, and decided to quit.** Then I remembered rule 1: **I am not here for tenure, so none of the advice actually applies to me…. and there are plenty of gender-neutral versions of that experience.** Instead I run a therapy couch for those male and female junior faculty who attend.

Final comments
When starting a lab....

Don’t worry about tenure!

Spend their money!

Enjoy what will probably be among the most exciting times of your career!